

CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY  
DEPARTMENT OF PESTICIDE REGULATION  
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA

Fluoxastrobin

Chemical Code # 5915, Tolerance # 52982  
SB 950 # NA

September 11, 2007

I. DATA GAP STATUS

<b>Chronic toxicity, rat:</b>	No data gap, no adverse effects
<b>Chronic toxicity, dog:</b>	No data gap, no adverse effects
<b>Oncogenicity, rat:</b>	No data gap, possible adverse effects
<b>Oncogenicity, mouse:</b>	No data gap, no adverse effects
<b>Reproduction, rat:</b>	No data gap, no adverse effects
<b>Teratology, rat:</b>	No data gap, no adverse effects
<b>Teratology, rabbit:</b>	No data gap, no adverse effects
<b>Gene mutation:</b>	No data gap, no adverse effects
<b>Chromosome effects:</b>	No data gap, no adverse effects
<b>DNA damage:</b>	No data gap, no adverse effects
<b>Neurotoxicity:</b>	No data gap, no adverse effects

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Toxicology one-liners are attached.

All record numbers through 233089 were examined.

\*\* indicates an acceptable study.

Bold face indicates a possible adverse effect.

## indicates a study on file but not yet reviewed.

File name: T091107

Revised by T. Moore, 9/11/07

## II. TOXICOLOGY ONE-LINERS AND CONCLUSIONS

These pages contain summaries only. Individual worksheets may contain additional effects.

### COMBINED, RAT

**\*\* 52982-0054; 229192;** "HEC 5725: Combined Study on Chronic Toxicity and Carcinogenicity in Wistar Rats (Dietary Administration for 2 Years)"; (L. Schladt, Ch. Ruhl-Fehlert; Bayer AG, PH-PD Toxicology, D-42096 Wuppertal, Germany; Report No. PH 31357; 9/13/01); Fifty Wistar rats/sex/group received HEC 5725 (batch no. 06261/0008; purity: 94.5% (6/98), 94.6% (1/99), 94.6% (7/99), 94.3% (12/99), 94.3% (4/00), 94.4% (5/00)) in the diet for two years. An additional 10 animals/sex/group were included in an interim sacrifice after one year of treatment. The male rats received 0, 40, 100, 1000 and 5000 ppm of the test material (0, 2.1, 5.2, 53.0, 271.9 mg/kg/day). The females received 0, 100, 500, 2500 and 12500 ppm of the test material (0, 6.9, 35.2, 181.3, 1083.2 mg/kg/day). Treatment did not affect the study animals' survival. The males in the 5000 ppm group and the females in the 12500 ppm group had lower mean body weights ( $p < 0.01$ ), (approximately 9 and 18% of the control value, respectively). There was no apparent treatment-related effect upon food consumption. The hematology evaluation did not indicate any treatment-related effects. The FOB did not reveal any treatment-related effects. In the clinical chemistry evaluation, the alanine aminotransferase activities and the total bilirubin concentrations in the serum of the 1000 and 5000 ppm males and the 2500 and 12500 ppm females were reduced in a dose-related manner in relation to the control values at various times during the study ( $p < 0.05$  or  $0.01$ ). However, the toxicological significance of the lower serum levels for these parameters was not apparent. In the urinalysis, the total phosphate recovered in the urine of the 5000 ppm males and the 12500 ppm females was less than that for the controls over the course of the study (NS,  $p < 0.05$  or  $0.01$ ). The total calcium recovered in the urine of the 12500 ppm females was likewise reduced in comparison to the controls (NS or  $p < 0.01$ ). At these higher treatment levels, the serum concentrations of phosphate and calcium were not affected by the treatment. The two ions were apparently being physiologically conserved. The mean relative liver weights of the 5000 ppm males and the 12500 ppm females were greater than the control values at both the interim sacrifice and at the termination of the study (NS,  $p < 0.05$  or  $0.01$ ). There was no corresponding histological lesion in the livers of these animals. Among the lesions noted in the histological examination, there was an increased incidence of mesenteric lymph nodes with increased numbers of mast cells (grades 2 and 3) in the 5000 ppm males and the 12500 ppm females ((M): 0: 4/48 vs. 5000: 18/49, (F) 0: 10/49 vs. 12500: 37/48,  $p < 0.01$ ). An increased incidence of myeloid hyperplasia was noted in the bone marrow of the 12500 ppm females (0: 2/50 vs. 12500: 11/50,  $p < 0.01$ ). The females in the 12500 ppm group also demonstrated an increased incidence of glandular hyperplasia in the uterus (0: 1/50 vs. 12500: 6/50). An increased incidence of adenocarcinoma was noted in the uterus of these animals as well (0: 3/50 vs. 12500: 10/49,  $p < 0.05$ ). The 20% incidence for this neoplastic lesion was outside the laboratory's range of historical control values (0 to 16.3%). **Possible adverse effect:** uterine adenocarcinoma. **Rat Chronic Dietary NOEL:** (M) 1000 ppm (53.0 mg/kg/day), (F) 2500 ppm (181.3 mg/kg/day) (based upon the lower mean body weights of the 5000 ppm males and the 12500 ppm females). **Possible oncogenicity:** uterine adenocarcinoma; **Study acceptable.** (Moore, 6/1/07)

### CHRONIC TOXICITY, RAT

See Combined, Rat above.

### CHRONIC TOXICITY, DOG

**\*\* 52982-0052; 229188;** "Technical Grade HEC 5725: A Chronic Toxicity Feeding Study in the Beagle Dog"; (R.D. Jones, T.F. Hastings; Bayer Corporation, Agriculture Division, Toxicology, Stilwell KS; Report No. 110920-1; 9/20/02); Four beagle dogs/sex/group received 0, 25, 50, 250, or 1200 ppm of Technical Grade HEC 5725 (batch no. 06261/0008, purity: 94.1% (7/99), 94.7% (4/00), 94.5% (8/00), 94.3% (3/01)) for 1 year ((M) 0, 0.8, 1.7, 8.1, 34.9 mg/kg/day; (F) 0, 0.7, 1.5, 7.7, 37.4 mg/kg/day). No deaths resulted from the treatment. The mean body weight gains of both sexes in the 1200 ppm group and the females in the 250 ppm group throughout the study were less than the control values. The mean food consumption of both sexes in the 1200 ppm

treatment group was generally less than that of the control group over the course of the study. The ophthalmology, hematology, urinalysis, neurological examination, and electrocardiography did not reveal any treatment-related effects. In the clinical chemistry evaluation, the serum creatinine levels for both sexes in the 1200 ppm group were lower than the control levels at various times during the study ( $p < 0.05$ ). The albumin concentrations in the serum of both sexes in the 1200 ppm group were lower than those of the controls throughout the study ( $p < 0.05$  or  $0.01$ ). The serum alkaline phosphatase activity of both sexes in the 1200 ppm group and the males in the 250 ppm group was significantly elevated in comparison to the control ( $p < 0.05$  or  $0.01$ ). The alanine aminotransferase and gamma glutamyl transpeptidase activities were elevated in the serum of both sexes in the 1200 ppm group throughout the study (NS or  $p < 0.05$  or  $0.01$ ). The mean absolute liver weights of both sexes in the 1200 ppm group and the mean relative liver weights of both sexes in the 1200 ppm group and the males in the 250 ppm group were greater than the control values ( $p < 0.05$ ). In the histopathological evaluation, hepatocytomegaly was noted in the livers of both sexes in the 250 and 1200 ppm groups ((M) 0: 0/4 vs. 250: 3/4 (severity: 2.0), 1200: 4/4 (severity: 2.0), (F) 0: 0/4 vs. 250: 2/4 (severity: 2.5), 1200: 3/4 (severity: 2.3). **No adverse indicated. Dog Chronic Dietary Toxicity NOEL:** (M/F) 50 ppm ((M) 1.7 mg/kg/day, (F) 1.5 mg/kg/day) (based upon the hepatocytomegaly noted in the livers of both sexes in the 250 ppm group). **Study acceptable.** (Moore, 5/25/07)

### ONCOGENICITY, RAT

See Combined, Rat above.

### ONCOGENICITY, MOUSE

\*\* 52982-0053; 229190; "HEC 5725: Oncogenicity Study in CD-1 Mice, Dietary Administration over 18 Months"; (R. Eiben; Bayer AG, PH-PD Toxicology, D-42096 Wuppertal, Germany; Study No. T5067480; 4/19/01); Fifty CD-1 mice/sex/group received 0, 100, 700 or 4200 ppm of HEC 5725 (batch no. 06261/0008; purity: 94.5% (6/98), 94.3% (4/00)) in the diet for 18 months ((M) 0, 18.5, 135.4, 775.6 mg/kg/day, (F) 0, 29.5, 204.0, 1265.1 mg/kg/day). The treatment did not affect the survival of the study animals. There was no treatment-related effect upon mean body weights and food consumption. The hematology data did not reveal any treatment-related effects. In the clinical chemistry data, the aspartate and alanine aminotransferase activities were lower in the serum of both sexes in the 700 and 4200 ppm groups at various times during the study (NS,  $p < 0.05$  or  $0.01$ ). However, the toxicologic significance of this effect was not apparent. The mean absolute and relative liver weights of both sexes in the 4200 ppm group and the mean relative liver weight of the males in the 700 ppm group were greater than the control values ( $p < 0.05$  or  $0.01$ ). In the histopathological examination, periportal/centrilobular hepatocytic hypertrophy was noted in the livers of the 4200 ppm females (0: 0/50 vs. 4200: 19/50,  $p < 0.01$ ). Eosinophilic changes in the hepatocytes of the 4200 ppm females was noted as well (0: 0/50 vs. 4200: 18/50,  $p < 0.01$ ). **No adverse effect evident. Mouse Chronic Dietary Toxicity NOEL:** (M/F) 700 ppm ((M) 135.4 mg/kg/day, (F) 204.0 mg/kg/day) (based upon the increased liver weights of both sexes in the 4200 ppm group and the incidence of the hepatocytic hypertrophy in the livers of the 4200 ppm females); **oncogenicity was not evident.** (Moore, 5/29/07)

### REPRODUCTION, RAT

\*\* 52982-0051; 229185, 229186; "A Two-Generation Reproductive Toxicity Study with HEC 5725 in the Wistar Rat"; (A.D. Young; Bayer CropScience LP, Toxicology, Stilwell KS and Crop Protection, Kansas City, MO and Pathology Associates International, Micropathology, Frederick, MD; Report No. 110249-1; 11/12/01, suppl. submission, 4/8/04); Thirty rats/sex/group in the P generation received 0, 100, 1000, or 10000 ppm of HEC 5725 technical (batch no. 06261/0008, purity: 94.6% (1/99), 94.1% (7/99), 94.7% (4/00), 94.5% (8/00)) in the diet for a 10 week pre-mating period, up to a 2 week mating period and 3 weeks both for the gestation and lactation periods. At that time, 30 F1 animals/sex/group were selected as parents and treated for an additional 10 weeks, followed by mating and 3 weeks each for gestation and lactation of the F2 generation. Parents in the 10000 ppm group of both generations had lower mean body weights than the control animals (NS,  $p < 0.05$  or  $0.01$ ). No treatment-related lesions were evident in the histopathological examination of the parental animals. No treatment-related effects were noted for the reproductive parameters. The mean pup body weights were less than those of the control

animals by day 21 of lactation for the 10000 ppm treatment groups in both generations ( $p < 0.01$ ). Incomplete ossification of the cranial calvaria was noted for the pups in the 10000 ppm group. Preputial separation was delayed in the F1 pups of the 10000 ppm group ( $p < 0.01$ ). No treatment-related effect was noted for the time to vaginal opening and ovarian follicle counts of the F1 female offspring or on spermatogenesis in the adult males of both generations. The calcium and phosphorus content in the femurs of the F1 pups was not affected by the treatment. **No adverse effects indicated. Parental NOEL:** 1000 ppm (based upon lower mean body weights for the adults in the 10000 ppm treatment group, (M) 73.7 mg/kg/day, (F) 86.7 mg/kg/day); **Reproductive NOEL:** 10000 ppm ((M) 763.6 mg/kg/day, (F) 871.3 mg/kg/day); **Developmental NOEL:** 1000 ppm (based upon lower mean pup weights during lactation period, (F) 170.6 mg/kg/day); **Study acceptable.** (Moore, 5/23/07)

#### TERATOLOGY, RAT

\*\* 52982-0158; 233083; "Developmental Toxicity Study with HEC 5725 in the Rat"; (H. Becker; RCC, Research & Consulting Company Ltd., CH 4452 Itingen, Switzerland, BRL Biological Research Laboratories Ltd., 4414 Fullinsdorf, Switzerland; Project No. 627884; 7/14/97); Twenty-five mated female Wistar rats/group were dosed orally by gavage with 0 (vehicle: aqueous 4% carboxymethylcellulose), 100, 300 or 1000 mg/kg/day of HEC 5725 technical (batch no. NLL 6112-8; purity: 98.9%) from gestation day 6 through gestation day 20. No maternal deaths resulted from the treatment. The mean body weights and food consumption were not affected by the treatment. The mean absolute and relative liver weights of the 1000 mg/kg dams were greater than the control values ( $p < 0.01$ ). There was no treatment-related effect upon the hepatic N-demethylase or O-demethylase activities and the cytochrome P450 content in the liver tissue or the other clinical chemistry parameters which were evaluated. No treatment-related lesions were noted in the necropsy examination. Fetal development was not affected by the treatment. **No adverse effect indicated. Maternal NOEL:** 300 mg/kg/day (based upon increased absolute and relative liver weights of the 1000 mg/kg dams); **Developmental NOEL:** 1000 mg/kg/day (based upon the lack of treatment-related effects in the 1000 mg/kg fetuses). **Study acceptable.** (Moore, 7/23/07)

#### TERATOLOGY, RABBIT

\*\* 52982-0163; 233089; "Developmental Toxicity Study in Rabbits after Oral Administration"; (B. Holzum; Bayer AG, Institute of Toxicology, D-42096 Wuppertal, Germany; Study No. T6062099; 9/16/99); Twenty two mated female CHBB:HM rabbits were dosed orally by gavage with 0, 25, 100 or 400 mg/kg/day of HEC 5725 technical (batch no. 06261/0008; purity: 94.5%) from days 6 to 28 of gestation. No mortality resulted from the treatment. Maternal food consumption was reduced during days 6 to 9 for both the 100 and 400 mg/kg/day treatment groups ( $p < 0.05$  and  $< 0.01$ , respectively). The number of fetuses with rib cartilage findings was increased in the 400 mg/kg group (0: 0/161 vs. 400: 6/141,  $p < 0.05$ ). Four litters in the 400 mg/kg group had fetuses suffering from this malformation. **No adverse effects indicated. Maternal NOEL:** 25 mg/kg/day (based upon reduced food consumption by does in the 100 mg/kg/day group), **Developmental NOEL:** 100 mg/kg/day (based upon the incidence of rib cartilage findings in the fetuses of the 400); **Study acceptable.** (Moore, 7/27/07)

#### GENE MUTATION

\*\* 52982-0160; 233085; "*Salmonella*/Microsome Test: Plate Incorporation and Preincubation Method"; (B. Herbold; Bayer AG, Toxicology, D-42096 Wuppertal, Germany; Study No. T-2053707; 6/20/96); *S. typhimurium* TA98, TA100, TA102, TA1535 and TA1537 strains were incubated with HEC 5725 technical (batch no. NLL 6112-4; purity: 98.9%) at levels ranging from 16 to 5000  $\mu\text{g}/\text{plate}$  (1<sup>st</sup> trial) or 10 to 3162  $\mu\text{g}/\text{plate}$  (2<sup>nd</sup> trial) under conditions of (-/+) activation and incubated for 48 hours at 37° C by means of the plate incorporation method (1<sup>st</sup> trial) or preincubation with the test material for 20 minutes prior to incorporation into the agar (2<sup>nd</sup> trial). Each treatment was cultured in triplicate. An Aroclor 1254-induced rat liver S9 fraction was used to metabolize the test material. There was no apparent treatment-related increase in the incidence of reverse mutation. The positive controls were functional. **No adverse effect indicated. Study acceptable.** (Moore, 7/24/07)

\*\* 52982-0161; 233086; "*Salmonella*/Microsome Test: Plate Incorporation and Preincubation Method"; (B. Herbold; Bayer AG, Toxicology, D-42096 Wuppertal, Germany; Study No. T0061472; 3/9/98); *S. typhimurium* TA98, TA100, TA102, TA1535 and TA1537 strains were incubated with HEC 5725 N technical (batch no. HUW 4202-3-3; purity: 99.7%) at levels ranging from 16 to 5000 µg/plate (both trials) under conditions of (-/+) activation and incubated for 48 hours at 37° C by means of the plate incorporation method. In the 2<sup>nd</sup> trial, the bacterial strains were preincubated with the test material for 20 minutes prior to incorporation into the agar. Each treatment was incubated in triplicate. An Aroclor 1254-induced rat liver S9 fraction was used to metabolize the test material. There was no apparent treatment-related increase in the incidence of reverse mutation. The positive controls were functional. **No adverse effect indicated. Study acceptable.** (Moore, 7/24/07)

\*\* 52982-0162; 233087; "Mutagenicity Study for the Detection of Induced Forward Mutations in the V79-HPRT Assay *In Vitro*"; (S. Brendler-Schwaab; Bayer AG, Toxicology, D-42096 Wuppertal, Germany; Study No. T 2053716; 1/7/97); Chinese hamster V79 cells were exposed to HEC 5725 technical (batch no. NLL 6112-4; purity: 98.9% (11/14/95), 99.4% (4/18/96)) at concentrations ranging from 1 to 200 µg/ml for 5 hours at 37° C with and w/o activation. Two trials were performed with duplicate cultures for each treatment level. An Aroclor 1254-induced rat liver S9 fraction was used to metabolize the test material. There was no treatment-related increase in the mutation frequency in either of the trials. **No adverse effect indicated.** The positive controls were functional. **Study acceptable.** (Moore, 7/25/07)

#### CHROMOSOME EFFECTS

\*\* 52982-0164; 233090; "*In Vitro* Mammalian Chromosome Aberration Test with Chinese Hamster V79 Cells"; (B. Herbold; Bayer AG, Toxicology, D-42096 Wuppertal, Federal Republic of Germany; Study No. T 0053705; 6/20/96); Chinese hamster V79 were exposed to HEC 5725 technical (batch no. NLL 6112-4; purity: 98.9% (11/14/95)) for 4 hours at 37° C. Cells were harvested at 18 or 30 hours after the beginning of the treatment. One trial was performed. Duplicate cultures were incubated for each treatment level. An Aroclor 1254-induced rat liver S9 fraction was used for activation. No treatment-related increase in the incidence of chromatid or chromosomal aberrations was noted. The positive controls were functional. **No adverse effect indicated. Study acceptable.** (Moore, 7/30/07)

#### DNA DAMAGE

\*\* 52982-0159; 233084; "Micronucleus-Test on the Male Mouse"; (B. Herbold; Bayer AG, PH-PD Toxicology, Carcinogenicity and Genotoxicity, D-42096 Wuppertal, Germany; Study No. T9059870; 1/14/99); Five male Hsd/Win mice/group were dosed twice by intraperitoneal (ip) injection with 0 (vehicle: aqueous 2% Cremophor), 75, 150 or 300 mg/kg of with a 24 hour interval between injections (note: an additional group of 5 males were treated with HEC 5725 technical (batch no. 06261/0008; purity: 94.5%). The animals were euthanized 24 hours after the second injection. A positive control group of five males also received a single ip injection with 20 mg/kg of cyclophosphamide and was euthanized at 24 hours post-dose. The femoral bone marrow was harvested and evaluated for the presence of micronuclei in both polychromatic and normochromatic erythrocytes. Two thousand polychromatic erythrocytes were evaluated per animal. Three of the 150 mg/kg animals died and were replaced in the study. Treatment-related signs included apathy, roughened fur, sternal recumbency, spasms, shivering, difficulty breathing and slitted eyes. There was no treatment-related increase in the number of micronuclei per 2000 polychromatic erythrocytes. The positive control was functional. **No adverse effect indicated. Study acceptable.** (Moore, 7/23/07)

#### NEUROTOXICITY

##### Acute Neurotoxicity

52982-0055; 229194; "An Acute Oral Neurotoxicity Screening Study with Technical Grade HEC 5725 in Wistar Rats"; (L.P. Sheets, R.G. Gilmore, B.P. Stuart; Bayer Corporation, Agriculture Division, Toxicology, Stilwell, KS, Experimental Pathology Laboratories Inc., Herndon, VA; Report No. 110509; 10/23/01); Twelve Wistar rats/sex/group were dosed orally by gavage with 0 (vehicle: aqueous 0.5% methylcellulose/0.4% Tween 80), 200, 500, or 2000 mg/kg of Technical Grade

HEC 5725 (batch no. 06261/0008; purity: 94.6% (1/99), 94.1% (7/99)). Functional observational battery and motor activity evaluations were performed prior to treatment, at 3 hours post-dose and on days 7 and 14. No deaths resulted from the treatment. There was no treatment-related effect upon mean body weights or FOB and motor activity determinations. In the histopathology examination, no treatment-related lesions were evident. **No adverse effect was indicated.** **Acute Neurotoxic NOEL:** (M/F) 2000 mg/kg (based upon the lack of treatment-related effects in the highest dose group); **Study acceptable.** (Moore, 6/8/07)

#### **Rat Subchronic Neurotoxicity Study**

52982-0056; 229916; "A Subchronic Neurotoxicity Screening Study with Technical Grade HEC 5725 in Wistar Rats"; (R.G. Gilmore, T.F. Hastings; Bayer CropScience LP, Toxicology, Stilwell, KS; Report No. 200366; 12/19/02); Twelve Wistar rats/sex/group received 0, 200, 1000 or 7500 ppm of Technical Grade HEC 5725 (batch no. 06261/0008; purity: 94.5% (8/00), 94.9% (8/01)) in the diet for 13 weeks ((M) 0, 12.7, 59.5, 473.9 mg/kg/day, (F) 0, 15.1, 71.7, 582.4 mg/kg/day). No deaths occurred during the study. The mean body weights of both sexes in the 7500 ppm group were lower than those of the control group over the course of the study (NS). There was no treatment-related effect upon the mean food consumption. The Functional Observational Battery and motor activity assessment and the ophthalmological examination did not reveal any treatment-related effects. In the necropsy examination, no treatment-related effect was noted upon the brain weights. In the micropathology, the males and females in the 7500 ppm group demonstrated an increased incidence of axonal degeneration, focal or multifocal, in the thoracic spinal cord ((M) 0: 2/6 (severity: 1.5) vs. 7500: 5/6 (severity: 1.0); (F) 0: 0/6 vs. 7500: 3/6 (severity: 1.3). However, these lesions involved a limited number of axons and no other levels of the spinal cord demonstrated a similar effect. **No adverse effect indicated.** **Rat Subchronic Neurotoxic NOEL:** (M/F): 7500 ppm ((M) 473.9 mg/kg/day, (F) 582.4 mg/kg/day) (based upon the lack of treatment-related neurotoxic effects noted for the animals in the 7500 ppm group); **Study acceptable.** (Moore, 6/11/07)

#### **METABOLISM**

52982-0057; 229198; "[Chlorophenyl-UL-<sup>14</sup>C]HEC5725: Rat Metabolism, Part 1 of 2: Toxicokinetic Behaviour and Metabolism in the Rat"; (A. Klempner; Bayer AG, Business Group Crop Protection, Development Department, Institute for Metabolism Research and Residue Analysis, 51368 Leverkusen, Federal Republic of Germany; Study No. M71819099; 3/5/02); Three studies were performed in which male Wistar rats were dosed orally by gavage with [Chlorophenyl-UL-<sup>14</sup>C]HEC5725 (lot nos. 12712/1 and 12712/5; radiochemical purity: > 99%, chemical purity: > 98%, specific radioactivity: 104.5 uCi/mg). Unlabeled HEC 5725, E-isomer (batch no. M0358, purity: 98.8%) was used to adjust the specific activity of the administered dose. In Studies No. 1 and 2, 4 animals were dosed with 1 mg/kg and urine and feces samples were collected up to 48 hours post-dose. In Study No. 5, 6 animals were dosed with 1 mg/kg and urine, feces and bile samples were collected up to 30 hours post-dose. Expired air was recovered up to 48 hours post-dose in Study No. 1 and plasma samples were drawn from the tail vein of animals up to 48 hours post-dose in Study No. 2. In Studies Nos. 1 and 2, the primary excretory route of radioactivity was via the feces with 76 to 77% of the administered dose recovered by 48 hours post-dose. Recovery in the urine constituted 13 to 14% of the administered dose. In Study No. 5, 77% of the radioactivity was recovered in the bile by 30 hours post-dose. An additional 3% was recovered in the urine and 11% in the feces. In Studies 1 and 2, approximately 1 to 2% of the radioactivity was retained in the tissues at 48 hours post-dose. For Study No. 5, 6% was retained in the tissues at 30 hours post-dose. Approximately 86% of the administered dose was absorbed. The liver, plasma, gastrointestinal tract and kidney were the primary tissues/organs in which the radioactivity was recovered at 48 hours post-dose. The radioactivity retained in the plasma did not appreciably decline over the 48 hours of sample collection. The principal metabolic reactions were the hydroxylation of the chlorophenyl ring to mono- and di-hydroxy moieties, followed by methylation or conjugation with glucuronic acid. Cleavage of the ether linkage between the pyrimidine and methoxyiminotolyl rings (rings 2 and 3), followed by oxidation and conjugation of the chlorophenyl and/or pyrimidine rings was observed as well. Twenty and 28% of the administered radioactivity in Studies No. 2 and 5, respectively,

was reported as characterized by HPLC with no additional identification provided. **Study acceptable.** (Moore, 6/21/07)

52982-0058; 229199; “[Chlorophenyl-UL-<sup>14</sup>C]HEC5725: Rat Metabolism, Part 2 of 2: Distribution of the Radioactivity in Male and Female Rats determined by Quantitative Whole Body Autoradiography”; (B. Neumann, E. Weber; Bayer AG, Crop Protection Business Group, Development Department, Institute for Metabolism Research and Residue Analysis, 51368 Leverkusen-Bayerwerk, Federal Republic of Germany; Study No. M71819099; 3/5/020); Eight Wistar rats/sex were dosed with 3 mg/kg of [Chlorophenyl-UL-<sup>14</sup>C]HEC5725 (lot nos. 12712/1, radiochemical purity: > 99%, chemical purity: > 98%, specific radioactivity: 104.5 uCi/mg). Unlabeled HEC 5725, E-isomer (batch no. M0358, purity: 98.8%) was used to adjust the specific activity of the administered dose. One animal/sex/time point was euthanized at 1, 4, 8, 24, 48, 72, 120 and 168 hours post-dose. Whole body autoradiographic procedures were used to quantify the radiolabel in specific tissues over the course of the study. Urine and feces were collected at specified time points from surviving animals through to the termination of the study. By 48 hours post-dose, greater than 95% of the administered dose was recovered in the excretory products. Feces constituted approximately 85 to 90% of the total recovered radiolabel. The highest concentrations of radiolabel were identified in the liver, renal medulla and cortex, brown and perirenal fat, the blood and the adrenal gland. The times-to-peak level were 4 hours for the liver and 4 to 8 hours for the kidneys, blood and adrenal gland. The concentration of label in the fat peaked at 1 hour post-dose. In the males, the urinary bladder demonstrated a high concentration of radiolabel at 4 and 8 hours post-dose. No appreciable radioactivity was localized in the central nervous system. **Study supplemental.** (Moore, 6/22/07)

52982-0059; 229201; “[Methoxyiminotolyl-ring-UL-<sup>14</sup>C]HEC5725: Rat Metabolism, Part 1 of 2: Toxicokinetic Behaviour and Metabolism in the Rat”; (A. Klempner; Bayer AG, Agricultural Division, Crop Protection Development, Institute for Metabolism Research and Residue Analysis, D-51368 Leverkusen, Federal Republic of Germany; Study No. M 21819076; 12/21/01); Nine tests were performed in which Wistar rats of either sex were dosed orally by gavage with 1 or 100 mg/kg of [methoxyiminotolyl-ring-UL-<sup>14</sup>C]HEC5725 (lot no. 11675/1 (test no. 1) and lot nos. 12250/1 and 12250/17 (test nos. 3 thru 12); radiochemical purity: > 98%, chemical purity: > 98%, specific radioactivity: 153 uCi/mg (test no. 1), 100 uCi/mg (test nos. 3 thru 12). Unlabeled HEC 5725, E-isomer (batch no. M00358, purity: 98.8%) was used to adjust the specific activity of the administered dose. In two of the tests, males or females were dosed daily for 14 days with 1 mg/kg of the unlabeled test material followed by a single dose of the labeled material. Expired air was recovered up to 72 hours post-dose in Test No. 1. Urine and feces samples were recovered at specified time intervals up to 24, 48 or 72 hours post-dose in all of the tests except for No. 6. Bile was collected up to 24 hours post-dose (test no. 9) and up to 48 hours post-dose (test no. 6). Plasma was recovered up to 48 hours post-dose in all tests except for Nos. 1,6 and 9. The primary excretory route of radioactivity was via the feces with 70 to 86% of the administered dose recovered by 48 hours post-dose. Recovery in the urine constituted 11 to 20% of the administered dose. There were no apparent differences arising from the different dosing regimens or between the sexes. In test no. 9, 87% of the radioactivity was recovered in the bile in the first 24 hours post-dose. An additional 5% was recovered in the urine and another 1 to 2% in the body. Approximately 92.2% of the administered dose was absorbed within the 1<sup>st</sup> 24 hours (estimated from bile and renal excretion data in study no. 9). In the other tests, approximately 0.2 to 0.5% % of the radioactivity was retained in the tissues at 48 hours post-dose. The liver was the primary organ in which radioactivity was recovered at 48 hours post-dose. The range of values for the pharmacokinetic parameters were as follows;  $t_{1/2}$  (absorption): 0.01 to 0.10 hours,  $t_{1/2}$  (elimination, phase 1): 0.72 to 4.09 hours,  $t_{1/2}$  (elimination, phase 2): 6.84 to 12.3 hours,  $t_{max}$ : 0.38 to 8.03 hours,  $C_{max}$ : (1 mg/kg treatment) 0.07 to 0.21 ug/ml, (100 mg/kg treatment) 2.33 and 2.91 ug/ml, volume of distribution: 8.9 to 17.1 liters. Metabolism of the parent compound included hydroxylation and methoxylation of the HEC 5725 molecule followed by conjugation with glucuronic acid. Hydrolysis of the ether linkage between the chlorophenyl ring (ring 1) and the pyrimidine ring (ring 2) resulted in the formation of HEC 5725 des chlorophenyl and associated derivatives. Eight to 20% of the administered radioactivity was reported as characterized by HPLC with no additional identification provided. **Study acceptable.** (Moore, 6/27/07)

52982-0060; 229202; “[Methoxyiminotolyl-ring-UL-<sup>14</sup>C]HEC5725: Rat Metabolism, Part 2 of 2: Distribution of the Radioactivity in Male and Female Rats determined by Quantitative Whole Body Autoradiography”; (B. Neumann, E. Weber; Bayer AG, Crop Protection Business Group, Development Department, Institute for Metabolism Research and Residue Analysis, 51368 Leverkusen-Bayerwerk, Federal Republic of Germany; Study No. M21819076; 12/21/01); Five Wistar rats/sex were dosed with 3 mg/kg of [Methoxyiminotolyl-ring-UL-<sup>14</sup>C]HEC5725 (lot nos. (test no. 5) 12250/1, (test no. 13) 12250/37, specific radioactivity: 100 uCi/mg, radiochemical and chemical purity: (test no. 5) > 98%, (test no. 13) > 99%). Unlabeled HEC 5725, E-isomer (batch no. M00358, purity: 98.8%) was used to adjust the specific activity of the administered dose. One animal/sex/time point was euthanized at 1, 4, 8, 24, and 48 hours post-dose. Whole body autoradiographic procedures were used to quantify the radiolabel in specific tissues over the course of the study. Urine and feces were collected at specified time points from surviving animals through to the termination of the study. By 24 hours post-dose, greater than 95% of the administered dose was recovered in the excretory products. Feces constituted approximately 75 to 80% of the total recovered radiolabel. The highest concentrations of radiolabel were identified in the urinary bladder and the liver over the 48-hour time course. The highest concentrations were recovered at 1 hour post-hour. No appreciable radioactivity was localized in the central nervous system. **Study supplemental.** (Moore, 6/29/07)

52982-0061; 229204; “[Pyrimidine-2-<sup>14</sup>C]HEC5725: Rat Metabolism, Part 1 of 2: Toxicokinetic Behaviour and Metabolism”; (B. Neumann; Bayer AG, Agrochemical Division, Crop Protection Development, Institute for Metabolism Research and Residue Analysis, 51368 Leverkusen, Federal Republic of Germany; Study No. M 61819098; 12/17/01); Two groups of four male Wistar rats/group were dosed with 1 mg/kg of [Pyrimidine-2-<sup>14</sup>C]HEC5725 (lot no. KML2621-A, specific radioactivity: 113.0 uCi/mg, radiochemical and chemical purity: > 98%) and urine and fecal samples were collected up to 48 hours post-dose. Expired air was recovered up to 48 hours post-dose in Test No. 1 and plasma samples were drawn from the tail vein of animals up to 48 hours post-dose in Test No. 2. The primary excretory route of radioactivity was via the feces with 72 to 73% of the administered dose recovered by 48 hours post-dose. Recovery in the urine constituted 12% of the administered dose. The liver, plasma and gastrointestinal tract were the primary tissues/organs in which the radioactivity was recovered at 48 hours post-dose. The peak plasma concentration of radiolabel was observed at 8 hours post-dose. No pharmacokinetic data were reported. The principal metabolic reactions were the hydroxylation of the chlorophenyl ring to mono- and di-hydroxy moieties. Cleavage of the ether linkage between the chlorophenyl moiety and the pyrimidine ring (rings 1 and 2) resulted in the HEC 5725 des-chlorophenyl metabolite. Cleavage of the ether linkage between the pyrimidine and methoxyiminotolyl rings (rings 2 and 3), followed by oxidation and conjugation of the chlorophenyl and/or pyrimidine rings was observed as well. Twenty two and 24% of the administered radioactivity in Test Nos. 1 and 2, respectively, was reported as characterized by HPLC with no additional identification provided. **Study supplemental** (study does not examine absorption profile of the test material despite the high percentage of excretion in the feces). (Moore, 7/3/07)

52982-0062; 229205; “[Pyrimidine-2-<sup>14</sup>C]HEC5725: Rat Metabolism, Part 2 of 2: Distribution of Radioactivity in Male and Female Rats determined by Quantitative Whole Body Autoradiography”; (B. Neumann, E. Weber; Bayer AG, Crop Protection Business Group, Development Department, Institute for Metabolism Research and Residue Analysis, 51368 Leverkusen-Bayerwerk, Federal Republic of Germany; Study No. M61819098; 12/17/01); Eight Wistar rats/sex were dosed with 3 mg/kg of [Pyrimidine-2-<sup>14</sup>C]HEC5725, lot no. 12216/1, specific radioactivity: 113 uCi/mg, radiochemical purity: >99%, chemical purity: > 98%). Unlabeled HEC 5725, E-isomer (batch no. M00358, purity: 98.8%) was used to adjust the specific activity of the administered dose. One animal/sex/time point was euthanized at 1, 4, 8, 24, 48, 72, 120 and 168 hours post-dose. Whole body autoradiographic procedures were used to quantify the radiolabel in specific tissues over the course of the study. Urine and feces were collected at specified time points from surviving animals through to the termination of the study. By 48 hours post-dose, greater than 100% of the administered dose was recovered in the excretory products. Approximately 90% of the total radiolabel which was recovered was in the feces. The highest concentration of radiolabel was identified in the liver. The time-to-peak level was 1 hour for the liver. The concentration of the

radiolabel in the urinary bladder varied over the first 8 hours post-dose. No appreciable radioactivity was localized in the central nervous system. **Study supplemental.** (Moore, 7/5/07)

52982-0063; 229206; “[Phenyl-UL-<sup>14</sup>C] 2-Chlorophenol: Absorption, Excretion and Metabolism in Male Rats”; (A. Klempner; Bayer AG, Business Group Crop Protection, Development Department, Institute for Metabolism Research and Residue Analysis, 51368 Leverkusen, Federal Republic of Germany; Study No. M 91819109; 3/4/02); Four male Wistar rats were dosed orally by gavage with 4.6 mg/kg of Phenyl-UL-<sup>14</sup>C] 2-Chlorophenol (no lot no., specific activity: 211.5 uCi/mg, radiochemical purity: > 98%, chemical purity: > 99%). Unlabeled 2-chlorophenol was used to adjust the specific activity of the dosing preparation. The test material was readily absorbed with the urine being the primary route of excretion. Ninety nine percent of the administered dose was recovered in the urine within 24 hours post-dose. The primary metabolites were the glucuronic acid and sulfate conjugates, 64 and 28% of the administered dose, respectively. Unmetabolized parent compound represented 3.7% of the administered dose. **Study supplemental.** (Moore, 7/9/07)

## SUBCHRONIC TOXICITY STUDIES

### Rat 4-Week Dietary Toxicity Study

52982-0066; 229209; “HEC 5725N: Study for Subacute Oral Toxicity in Rats (Feeding Study over 4 Weeks)”; (F. Krotlinger, E. Hartmann; Bayer AG, Toxicology, D-42096 Wuppertal, Germany; Study No. T2062329; 9/14/99); Five Wistar rats/sex/group received 0, 100, 500, 2500 or 10000 ppm of HEC 5725 N technical (batch no. NLL 6112-24; purity: 99.3%) in the diet for 4 weeks ((M) 0, 9.7, 49.9, 237.1, 1016.8 mg/kg/day, (F) 0, 8.6, 43.4, 221.6, 891.8 mg/kg/day). No deaths occurred during the study. The mean body weights of the females in the 10000 ppm group were lower than those of the control throughout the study ( $p < 0.05$  or  $0.01$ ). The mean food consumption of the 2500 and 10000 ppm females was less than that of the controls over the course of the study (NS). No effect on water consumption was noted. In the hematology evaluation, the hemoglobin concentration of both sexes in the 10000 ppm group was less than that of the controls ( $p < 0.01$ ). The mean hematocrit of the 500 ppm females and above was less than that of the controls ( $p < 0.05$  or  $0.01$ ). In the clinical chemistry evaluation, the serum urea concentration was elevated for both sexes in the 10000 ppm group ( $p < 0.01$ ). The hepatic N-demethylase activity of both sexes in the 500 ppm group and above was lower than that of the controls (NS,  $p < 0.05$  or  $0.01$ ). In the urinalysis, the calcium and oxalic acid concentrations and the amount of both which were excreted by the males in the 10000 ppm group were greater than the control values. The calcium concentration and amount excreted was also elevated for the 10000 ppm females. The mean relative liver weights of both sexes in the 10000 ppm group were greater than those of the controls ( $p < 0.01$ ). No treatment-related lesions were noted in the histopathological examination. The various immunotox parameters which were evaluated did not reveal any apparent treatment-related effect. **No adverse effect indicated. Rat 4-Week Dietary NOEL:** (M/F) 100 ppm ((M) 9.7 mg/kg/day, (F) 8.6 mg/kg/day) (based upon the lower hepatic N-demethylase activity of the 500 ppm males and the lower hematocrit of the 500 ppm females). **Study supplemental,** (non-guideline study). (Moore, 7/19/07)

52982-0065; 229208; “HEC 5725 & HEC 5725A: Comparative Study for Subacute Oral Toxicity in Rats (Feeding Study for 4 Weeks)”; (P. Andrews; Bayer AG, Toxicology, 42096 Wuppertal, Germany; Study No. T707811; 2/28/02); Five Wistar rats/sex/group received 0, 100, 500, 2500 or 10000 ppm of HEC 5725 technical (batch no. 06261/0008, purity: 95.1% (98.8% E-isomer, 1.2% Z-isomer) or HEC 5725A technical, batch no. NLL 6112-31, purity: 97.7% (62.5% E-isomer, 35.2% Z-isomer) in the diet for 4 weeks (HEC 5725: (M) 0, 8.3, 41.5, 209.7, 1005.6 mg/kg/day, (F) 0, 10.0, 52.7, 261.2, 1451.7 mg/kg/day, HEC 5725A: (M) 0, 8.5, 42.1, 226.6, 1001.5 mg/kg/day, (F) 0, 8.8, 47.7, 247.6, 1419.5 mg/kg/day). No deaths resulted from the treatment. The mean body weight of the males of both 10000 ppm treatment groups demonstrated lower mean body weights by the termination of the study (NS). No treatment-related effect upon food or water consumption was evident. The hematology evaluation and urinalysis did not reveal any treatment-related effects. In the clinical chemistry evaluation, the serum phosphorus levels of both sexes in both 2500 and 10000 ppm groups were lower than those of the control group (NS,

$p < 0.05$  or  $0.01$ ). The mean serum albumin level of both sexes in the HEC 5725 10000 ppm group were greater than those of the control ( $p < 0.05$  or  $0.01$ ). The mean hepatic N-demethylase activities of both sexes in the HEC 5725 500 ppm group and above and the males in the HEC 5725 500 ppm group and above were lower than those of the control ( $p < 0.05$  or  $0.01$ ). For the 2500 and 10000 ppm females in the HEC 5725A group, the activity for this enzyme was also lower than that of the control group ( $p < 0.01$ ). (Note: the historical control value reported for the males was used in making this assessment). The mean absolute and relative organ weights did not demonstrate any apparent treatment-related effect. In the histopathological evaluation, cytomegaly was noted in the adrenal gland of both sexes of both 10000 ppm treatment groups and the females in the 2500 ppm group ((M) 0: 1/5, HEC 5725, 10000: 3/5, HEC 5725A, 10000: 3/5, (F) 0/5 vs. HEC 5725: 2500: 1/5, 10000: 4/5 ( $p < 0.05$ ), HEC 5725A: 2500: 1/5, 10000: 3/5). **No adverse effect indicated. Rat 4-Week Dietary NOEL:** (M) 100 ppm (HEC 5725: 8.3 mg/kg/day, HEC 5725A: 8.5 mg/kg/day) (based upon reduced hepatic N-demethylase activity for the males in the 500 ppm treatment groups); (F) 500 ppm (HEC 5725: 52.7 mg/kg/day, HEC 5725A: 47.7 mg/kg/day) (based upon the cytomegaly noted in the adrenals of the females in 2500 ppm groups); **Study supplemental** (non-guideline study). (Moore, 7/18/07)

### **Rat Subchronic Dietary Toxicity Study**

52982-0047; 229178; "Study on Subchronic Toxicity in Wistar Rats. Dietary Administration over 2 Months."; (Leser, K.H., Hartmann, E.; Bayer AG, PH-PD Toxicology, Carcinogenicity and Genotoxicity, D-42096 Wuppertal, Germany; Study No. T3062320; 6/6/01); Ten Wistar rats/sex/group received HEC 5725 (batch no. NLL6112-(20-22); purity: 97.1%) in the diet for 9 weeks. The males received 0, 62.5, 125, 1000, or 8000 ppm of the test material (0, 3.6, 7.3, 59.7, 520.3 mg/kg/day). The dietary preparations for the females had 0, 125, 250, 2000 or 16000 ppm of the test material (0, 9.0, 18.3, 146.3, 1544.2 mg/kg/day). In addition, 10 animals/sex/group received 1%  $\text{NH}_4\text{Cl}$  in the drinking water. The males received either 0 or 8000 ppm of the test material in their diet (0, 476.5 mg/kg/day). The females were dosed with 0 or 16000 ppm in the diet (0, 1590.6 mg/kg/day). There were no treatment-related deaths during the study. There was no apparent treatment-related effect upon the mean body weights or food and water consumption. In the clinical chemistry evaluation, the plasma albumin concentration was increased for the males in the 8000 ppm group (main and satellite study at 4 weeks and for the 16000 ppm females (main study only) at 7 weeks ( $p < 0.01$ ). The citric acid and calcium concentrations in the plasma of the 1000 and 8000 (main and satellite) ppm males were increased over those of the control at 4 weeks ( $p < 0.05$  or  $0.01$ ). This increase in the citric acid concentration persisted in the 8000 ppm (main and satellite) group and for the calcium concentration in the 8000 ppm (satellite only) at 8 weeks ( $p < 0.01$ ). For the females, the citric acid concentrations were increased in the 2000 and 16000 ppm (main and satellite) females at 4 weeks and for the 16000 ppm (satellite) group at 7 weeks ( $p < 0.01$ ). The plasma calcium concentrations were increased for the 2000 and 16000 (main only) ppm groups at both 4 and 7 weeks ( $p < 0.05$  or  $0.01$ ). The plasma phosphate concentration was lower for the 1000 and 8000 (main and satellite) ppm males at 4 weeks (NS,  $p < 0.05$  or  $0.01$ ). No treatment-related effect was evident on the parathyroid hormone or vitamin D3 concentrations in the plasma for either sex after 4 or 8 weeks of treatment. In the urinalysis, the pH was increased for the males in the 1000 and 8000 (main) ppm groups at 4 weeks and for the males in the 8000 (main only) ppm group at 8 weeks ( $p < 0.5$  or  $0.01$ ). The pH value for the 2000 and 16000 (main only) ppm females was also greater at 5 weeks ( $p < 0.01$ ). The urinary calcium concentrations were increased for the 1000 and 8000 (main and satellite) ppm males at both 4 and 8 weeks (NS or  $p < 0.01$ ). The concentrations of phosphate in the urine of the 1000 and 8000 (main and satellite) ppm males were less than the control values at both 4 and 8 weeks ( $p < 0.05$  or  $0.01$ ). The urinary calcium concentration of the 16000 (main only) ppm females was greater than that of the control after 5 weeks of treatment (NS). The urinary phosphate concentration was decreased for the 16000 (satellite only) ppm females at 5 weeks ( $p < 0.01$ ). No treatment-related effect was evident on the cAMP concentration in the urine of either sex after 4 or 8 weeks of treatment. In the necropsy examination, only the kidneys of the males in the 8000 ppm satellite group had an increased organ/body weight ratio in comparison to the satellite control group ( $p < 0.05$ ). There was an increased incidence of small vacuoles in the adrenal cortex of the 1000 and 8000 (main and satellite) ppm males (0: 1/10 vs. 1000: 3/10, 8000 (main): 6/10, (satellite): 5/10). Calcium deposition in the bone was not affected by the treatment. In the

toxicokinetic study, the presence of the parent compound in the plasma was below the limits of detection for the 8000 ppm males. For the 16000 ppm females, the concentration of the parent compound averaged 0.3 ug/ml for each of the time points. The presence of polar metabolites in the plasma of both sexes was noted. **No adverse effect indicated. Rat Subchronic Dietary Toxicity NOEL:** (M) 125 ppm (7.3 mg/kg/day), (F) 250 ppm (18.3 mg/kg/day) (based upon increased citric acid and calcium concentrations in the plasma of the males in the 1000 ppm group and of the females in the 2000 ppm group); **Study supplemental**, (not a guideline study). (Moore, 5/16/07)

#### **Dog Subchronic Dietary Toxicity Study**

52982-0048; 229180; "Technical Grade HEC 5725: A Low-Dose Subchronic Toxicity Feeding Study in the Beagle Dog"; (R.D. Jones, T.F. Hastings; Bayer Corporation, Agriculture Division, Toxicology, Stilwell, KS; Report No. 110819; 11/5/01); Four beagle dogs/sex/group received 0, 25, or 50 ppm of Technical Grade HEC 5725 (batch no. 06261/0008; purity: 94.1% (7/99), 94.7% (4/00), 94.3% (3/01) for 90 days ((M) 0, 0.7, 1.4 mg/kg/day; (F) 0, 0.7, 1.5 mg/kg/day). No deaths resulted from the treatment. There was no treatment-related effect upon the mean body weights and food consumption. The ophthalmology, hematology, clinical chemistry, urinalysis and the neurological examination did not reveal any treatment-related effects. Assay of various liver enzymes at the termination of the study did not reveal any treatment-related effects. The mean relative liver weights of the both sexes in the 50 ppm group were greater than the control values ( $p < 0.05$ ). However, no histopathological lesion was noted which correlated with these weight increases. **No adverse indicated. Dog Subchronic Dietary Toxicity NOEL:** (M/F) 50 ppm ((M) 1.4 mg/kg/day, (F) 1.5 mg/kg/day) (based upon the lack of a treatment-related effect in the 50 ppm group). **Study acceptable.** (Moore, 5/21/07)

52982-0049; 229181; "Technical Grade HEC 5725: A Subchronic Toxicity Feeding Study in the Beagle Dog"; (R.D. Jones, L.E. Elcock; Bayer Corporation, Agriculture Division, Toxicology, Stilwell, KS; Report No. 111012; 11/5/01); Four beagle dogs/sex/group received 0, 100, 800 or 3000 ppm of Technical Grade HEC 5725 (batch no. 06261/0008, purity: 94.5% (6/98), 94.6% (1/99), 94.1% (7/99)) for 90 days. The concentration in the highest treatment group was adjusted from 3000 to 2500 ppm on the 8<sup>th</sup> study day due to reduced food consumption by the animals in that study group ((M) 0, 3.0, 24.8, 76.0 mg/kg/day; (F) 0, 3.0, 24.2, 75.0 mg/kg/day). No deaths resulted from the treatment. The mean body weights and food consumption of both sexes in the 3000 ppm group were lower than the control values during the 1<sup>st</sup> week of the study. Thereafter, there was no apparent treatment-related effect upon either parameter through the remainder of the study. The ophthalmology, hematology, urinalysis, neurological examination, and electrocardiography did not reveal any treatment-related effects. In the clinical chemistry evaluation, the serum creatinine and cholesterol levels for both sexes in the 2500 ppm group and the males in the 800 ppm group had been lower than the control levels at various times during the study ( $p < 0.05$ ). The albumin concentrations in the serum had been lower for both sexes in the 2500 ppm group throughout the study ( $p < 0.05$ ). By the conclusion of the study, the serum alkaline phosphatase activity of both sexes in the 2500 ppm group was significantly elevated in comparison to the control ( $p < 0.05$ ). Assay of various liver enzymes at the termination of the study revealed an increased level of activity for the males in all of the treatment groups and for the females in the 800 and 2500 ppm treatment groups ( $p < 0.05$ ). The concentration of cytochrome P450 protein in the livers was increased for both sexes in all of the treatment groups ( $p < 0.05$ ). The UDP-glucuronyltransferase activity was increased in the livers of both sexes in the 2500 ppm group and the females in the 800 ppm group (NS,  $p < 0.05$ ). The mean absolute liver weight of the males in the 2500 ppm group and the mean relative liver weights of both sexes in the 2500 ppm group and the males in the 800 ppm group were greater than the control values ( $p < 0.05$ ). The mean relative kidney weights of the females in the 800 and 2500 ppm group and the mean absolute and relative pituitary weights of the females in all of the treatment groups were greater than the control values ( $p < 0.05$ ). In the histopathological evaluation, hepatocytomegaly was noted in the livers of both sexes in the 800 and 2500 ppm groups ((M) 0: 0/4 vs. 800: 3/4 (severity: 1.0), 2500: 4/4 (severity: 2.8), (F) 0: 0/4 vs. 800: 3/4 (severity: 2.0), 2500: 4/4 (severity: 3.0). Swelling of the proximal tubules was noted in the kidneys of the males in the 2500 ppm group (0: 0/4 vs. 2500: 3/4 (severity: 1.3)). **No adverse indicated. Dog Subchronic Dietary**

**Toxicity NOEL:** (M/F) < 100 ppm ((M/F) < 3.0 mg/kg/day) (based upon the induction of cytochrome P450 in the liver of both sexes in the 100 ppm group). **Study acceptable.** (Moore, 5/18/07)

#### **Rat Repeated Dosing Dermal Toxicity Study**

52982-0050; 229183; "HEC 5725: Study for Subacute Dermal Toxicity in Rats (four-week treatment period)"; (F. Krotlinger, A. Popp; Bayer AG, Toxicology, D-42096 Wuppertal, Germany; Study No. T1069312; 11/22/00); The skin of 10 Wistar rats/sex/group was exposed to 0, 100, 300 or 1000 mg/kg/day of HEC 5725 (batch no. 06261/0008, purity: 94.3%) 6 hours/day, 5 days per week for 3 weeks followed by another week of 6 hours/day. The test material was placed on a piece of gauze moistened with water and the gauze was placed on the skin. No deaths resulted from the treatment. The mean body weights or food consumption were not affected by the treatment. The hematology, clinical chemistry, and ophthalmology evaluations did not reveal any treatment-related effects. There was no effect upon the absolute or relative organ weights in the necropsy examination. No treatment-related lesions were noted in the histopathology. No dermal lesions were evident at the site of application. **No adverse effect indicated. Reported Rat Repeated Dosing Dermal Toxicity NOEL:** (M/F) 1000 mg/kg/day (based upon the lack of treatment-related effects on the 1000 mg/kg treatment group); **Reported Dermal Irritation NOEL:** (M/F) 1000 mg/kg/day (based on the lack of dermal irritation at the site of application on the 1000 mg/kg treatment group); **Study unacceptable**, possibly upgradeable to acceptable with a more detailed description of how the test material was moistened. (Moore, 5/21/07)

#### **Mouse Immunotoxicity Study**

52982-0064; 229207; "Study for Subacute Oral Toxicity in Mice (Feeding Study for 5 weeks - Immunotoxicity Investigations)"; (P. Andrews, H.W. Vohr; Bayer AG, Toxicology, 42096 Wuppertal, Germany; Study No. T 7070398; 10/16/01); Eight CRL: CD1(ICR) mice/sex/group received 0, 450, 1800 or 7000 ppm of HEC 5725 technical (batch no. 06261/0008; purity: 94.2%) in the diet for 5 weeks (reported uptake of active ingredient: (M) 0, 106.8, 367.3, 1543.4 mg/kg/day, (F) 0, 157.3, 659.6, 2383.3 mg/kg/day). No deaths resulted from the treatment. No treatment-related effect upon the mean body weights or food consumption was evident. No treatment-related clinical signs were noted. The number of cells per spleen was not affected by the treatment. The Plaque-Forming Cell assay did not reveal any suppression of the T-cell mediated IgM response in the spleen of the treated animals. **Study unacceptable**, possibly upgradeable to acceptable with the submission of the positive control study data cited in the report. (Moore, 7/11/07)